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EXAMINER	
GANGLE, BRIAN J	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,753	PIZZA, MARIAGRAZIA	
	Examiner	Art Unit	
	Brian J. Gangle	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,6,8,10,12,14-19,22-26,28 and 32-34* is/are pending in the application.

4a) Of the above claim(s) *15-19,22-25 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,6,8,10,12,14,26 and 32-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/13/2009, 1/8/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment and remarks filed 12/14/2009 are acknowledged. Claim 4 is amended. Claims 1-3, 5, 7, 9, 11, 13, 20, 21, 27, and 29-31 are cancelled. New claims 32-34 are added. Claims 4, 6, 8, 10, 12, 14-19, 22-26, 28, and 32-34 are pending. Claims 15-19, 22-25, and 28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 8/29/2007. Claims 4, 6, 8, 10, 12, 14, 26, and 32-34 are currently under examination.

Information Disclosure Statement

The information disclosure statements filed on 7/13/2009 and 1/8/2010 have been considered. Initialed copies are enclosed.

Claim Rejections Maintained

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4, 6, 8, 10, 12, 14, 26, and newly submitted claims 32-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is maintained for the reasons set forth in the previous office action in the rejection of claims 4, 6, 8, 10, 12, 14, and 26.

The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant argues:

1. That, while the examiner has asserted that the specification and claims do not place any limit on the number of amino acid substitutions, insertions, and/or deletions that may be

made in the proteins listed, instead, the five claimed proteins are clearly limited by being capable of inducing a bactericidal antibody response.

2. That the five proteins have been described in detail in the instant specification or in references incorporated by reference. Applicant refers to WO03/020756, which includes data from testing several variants of GNA2132 against different strains and found similar levels of immune response for each. Applicant thus asserts that, one of skill in the art generating the five meningococcal antigens would not generate random and irrelevant variants, especially since the instant specification provides guidance and references to each of the five antigens and hybrids thereof. Applicant states that they disagree with the examiner's assertion that the practice of the composition of claim 4 would require that one of skill in the art generate an almost infinite number of random polypeptides, because one of ordinary skill would not blindly generate any proteins, but would instead refer to the instant specification and the cited references and take into account the limitation that these antigens need to be capable of producing a bactericidal antibody response.

3. That *Falkner v. Inglis* supports applicant's position. Applicant states that in Falkner, the court recognized that the teachings of the invention could be applied to the creation of a poxvirus even though the disclosed embodiment was a herpesvirus. Applicant also notes that the court stated that one would be able to use the lessons of the application regarding the herpesvirus to construct a similar poxvirus. Applicant argues that the instant application actually teaches the combination of five disclosed antigens and refers to earlier applications which include further details of the antigens, unlike in Falkner.

4. That based on the guidance in the specification and the cited reference, only limited experimentation, if any, would be required to generate numerous variations of the five antigens capable of generating the claimed response.

5. That a representative number of variants has been described because the preferred forms of the five antigens are described in the specification and additional variants have been cited in references 14-16.

6. That the NMBxxxx designations based on Tettelin provide a clearly defined link to supplemental material available online and to corresponding sequences deposited in GenBank. Applicant argues that a search of GenBank for NadA reveals entries such as AAF42321, thus one

of skill in the art can readily recognize the metes and bounds of a claim that names an adhesion-specific protein using the NMBxxxx nomenclature instead of a SEQ ID. Applicant argues that the NCBI databases are well curated, that changes can be tracked, and that it is illegal to make unauthorized changes to the GenBank database.

Applicant's arguments have been fully considered and deemed non-persuasive.

Regarding argument 1, applicant's assertion is misleading and is not relevant to whether the claims has sufficient written description support. It is true that the proteins encompassed by the claims are limited to those which are capable of inducing a bactericidal antibody response. However, there are nowhere near 5 proteins encompassed by the claims. As stated by the examiner, specification and claims do not place any limit on the number of amino acid substitutions, insertions, and/or deletions that may be made. Use of the term "variants thereof" places absolutely no restriction on the structure of the proteins encompassed such that the claims (at least the broadest claims) define the invention by function alone. While there are narrower claims, most of these only place a structural requirement on a single protein at a time and others recite a particular percent identity. Neither the claims nor the specification provide any correlation between the claimed structure and the claimed function.

Regarding argument 2, applicant's argument is insufficient for several reasons. First, the instant application does not properly incorporate any material by reference. To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents. *See In re Seversky* , 474 F.2d 671, 674, 177 USPQ 144, 146 (CCPA 1973) (providing that incorporation by reference requires a statement "clearly identifying the subject matter which is incorporated and where it is to be found"). Applicant has simply added a sentence at the beginning of a list of references and claimed that said references are incorporated by reference. Second, applicant is arguing that the material contained within those references is part of what is necessary to provide written description of the claimed subject matter. Therefore, said material is "essential material" which may be incorporated by reference, but only by way of an incorporation by reference to a U.S. patent or U.S. patent application publication, which patent or patent application publication does not itself incorporate such essential material by reference. Third, reference 16 (WO03/020756) was not published until March 13, 2003, which is after the

instant priority date. The claims require written description as of the filing date. Therefore, post-filing references cannot supply material necessary for written description. Fourth, the requirement for written description is separate from the enablement requirement. How much work on of skill in the would have to do to obtain the claimed invention is not relevant. It is relevant, however, that applicant acknowledges that one of skill in the art would have to test variants to determine whether they had the appropriate function. Since one of skill in the art would have had to test variants in this manner, they clearly were not disclosed by applicant and thus could not have been in applicant's possession at the time of filing.

Regarding argument 3, applicant is confusing the findings of the court in Falkner with regard to enablement and the findings with regard to written description. It is true that the court stated that one would be able to use the lessons of the application regarding herpesvirus to construct a similar poxvirus. However, this statement was only applicable to the enablement rejection. Whether or not one could make the invention is not a part of the written description question. In written description, the question is whether applicant had possession of the invention. With regard to written description, the court found that the specification devoted several passages to poxviruses and articles describing essential genes for poxvirus were well-known in the art. This is not related to the instant case where it is completely unpredictable what changes can be made to the unlimited proteins encompassed and still have the required function. It is simply not the number of possibilities that is the issue; it is the complete lack of correlation between structure and function that creates the issue. In fact, applicant themselves have argued this. Applicant has argued that, even knowing the specific antigens in the instant application, one cannot predict the results of their combination. In their arguments of 12/30/2008, applicant states that the specific antigens combined synergistically rather than additively and some combinations produced a less than additive response. Applicant has argued that the results of Guliani *et al.* show surprising and unexpected results with the specific combination of NadA and two fusion proteins ('953-'287 and '741-'936). The art shows that the results of amino acid changes on the immune response are completely unpredictable and even Giuliani *et al.* support this, showing that NadA did not perform well when fused to other proteins. This is exactly as one would expect considering how conformational changes alter antibody binding. Thus, fusing proteins together or altering their amino acid sequence in any way alters the immune response

generated. This unpredictability shows that there is no way to predict the outcome of amino acid changes. Therefore, *any* variant, whether 20% 80%, or 95% identical to the original sequence might or might not have the appropriate bactericidal response. In fact, even the compositions of claim 34, which provides specific SEQ ID NOs for the five antigens, cannot be presumed to have the correct activity because these five antigens can be present in many ways including as separate proteins or fusions different than those shown in the specification to be effective. As stated by applicant, "the specification does not teach that the individual antigens would provide this coverage" and "even with the superior antigens identified by the inventors in the instant specification, the results are clearly not additive."

The issues in *Ex Parte Kubin* and *In re Kubin* are much more closely related to the instant case than Falkner. In these cases, the claims encompassed variants with a specific percent identity. The Board found that "[Appellants] have not described what domains of those sequences are correlated with the required binding to CD48, and thus have not described which of NAIL's amino acids can be varied and still maintain binding. Thus … their Specification would not have shown possession of a sufficient number of sequences falling within their potentially large genus to establish possession of their claimed genus. Without a correlation between structure and function, the claim does little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement." This is precisely the situation in the instant case.

Regarding argument 4, applicant is correct that it would only require limited experimentation to generate variants that have the correct response. However, having a variant with the correct activity is different than knowing whether the variant has the activity. Generating variants is simple. But, as shown by the art there is no correlation whatsoever between the required activity and the structures in the claims. Any variant might or might not have the required activity, but there is no way to know ahead of time that it would, as the results of changes are completely unpredictable. The structure set forth in the claims encompasses a virtually unlimited number of peptides, and applicant has not shown which of these has the required function.

Regarding argument 5, both the art and applicant's arguments show that the activity of a given fusion protein or variant is unpredictable. Therefore, unless a particular composition has

been shown to have the correct effect, one cannot know whether it would or not. Because of this basic immunological fact, only one embodiment has been shown. Unless applicant is asserting that the compositions disclosed in the prior art references read on the instant claims as prior art, one cannot take what they have learned from those references and apply it to other compositions. Furthermore, as stated above, references 14-16 cannot be relied upon to provide written description.

Regarding argument 6, applicant cannot rely on GenBank for written description support because "essential material" may be incorporated by reference, but only by way of an incorporation by reference to a U.S. patent or U.S. patent application publication, which patent or patent application publication does not itself incorporate such essential material by reference. Moreover, as applicant points out, there are multiple sequences associated with NMB designations, for example, a search of GenBank using the NMBxxxx nomenclature for NadA reveals *entries* such as AAF42321. Therefore, these designations do not refer to any particular protein, but instead to multiple variants, which applicant has not described.

As outlined previously, the rejected claims are drawn to compositions comprising five meningococcal antigens, wherein the composition is able to induce a bactericidal antibody response against hypervirulent lineages A4, ET-5, and lineage 3 of *N. meningitidis* serogroup B. Dependent claims limit the composition to where an "NadA" protein, a "NMB1870" protein, a "NMB2091" protein, a "NMB1030" protein, and a "NMB2132" protein, or variants thereof. In addition, there are claims drawn which list the "NadA" protein as SEQ ID NO:2; the "NMB1870" protein as SEQ ID NO:3; the "NMB2091" protein as SEQ ID NO:4; the "NMB1030" protein as SEQ ID NO:5; and the "NMB2132" protein as SEQ ID NO:6.

The claims are drawn to an unlimited genus of immunogenic compositions comprising polypeptides that are capable of inducing a bactericidal antibody response against hypervirulent lineages A4, ET-5, and lineage 3 of *N. meningitidis* serogroup B. To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from

others, so as to reasonably convey to the skilled artisan that applicant has possession the claimed invention. To adequately describe the genus of immunogenic compositions comprising the claimed composition, applicant must adequately describe the antigenic determinants (immunoepitopes) that elicit the induction of bactericidal antibodies directed against two or more strains of hypervirulent lineages A4, ET-5, and lineage 3 strains of serogroup B *N. meningitidis*, not just those determinants that would elicit an immune response to the said polypeptides since a given polypeptide can be immunogenic but not induce a bactericidal antibody response directed against two or more strains of hypervirulent lineages A4, ET-5, and lineage 3 strains of serogroup B *N. meningitidis.*

The specification discloses a composition comprising an NadA polypeptide with the sequence of SEQ ID NO:2, a fusion protein with the sequence of SEQ ID NO:7 (a fusion of SEQ ID NOs 6 and 5), and a fusion protein with the sequence of SEQ ID NO:8 (a fusion of SEQ ID NO:4 and 3). This composition satisfies the written description requirements. Applicant has not demonstrated that any other composition, including variants of the above composition, is capable of inducing a bactericidal antibody response directed against two or more strains of hypervirulent lineages A4, ET-5, and lineage 3 strains of serogroup B *N. meningitidis.* The specification further does not disclose distinguishing and identifying features of a representative number of members of the genus of immunogenic compositions to which the claims are drawn, such as a correlation between the structure of the immunoepitope and its recited function (i.e. eliciting the recited immune response), so that the skilled artisan could immediately envision, or recognize at least a substantial number of members of the claimed genus of immunogenic compositions. Moreover, the specification fails to disclose which amino acid residues are essential to the function of the immunoepitope or which amino acids might be replaced so that the resultant immunoepitope retains the activity of its parent, or by which other amino acids the essential amino acids might be replaced so that the resultant immunoepitope retains the activity of its parent. Therefore, since the specification fails to adequately describe at least a substantial number of members of the genus of immunoepitopes to which the claims are based; the specification fails to adequately describe at least a substantial number of members of the claimed genus of immunogenic compositions that elicit the induction of bactericidal antibodies directed

against two or more strains of hypervirulent lineages A4, ET-5, and lineage 3 strains of serogroup B *N. meningitidis*.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016.

Because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

The *Guidelines* state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus"; accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the

genus. As evidenced by Greenspan *et al.* (Nature Biotechnology 7: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan *et al.* recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan *et al.*, an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows that the immunoepitopes that can elicit a protective immune response to a given pathogen can only be identified empirically.

As taught in basic immunology texts, an epitope or antigenic determinant interacts with its corresponding antibody based on the three-dimensional structure of both molecules and the fit between them (Cruse *et al.*, Illustrated Dict. of Immunology, 2nd ed., CRC Press, 2003, page 46). These epitopes can be conformational (or discontinuous) epitopes which are formed from separate regions in the primary sequence that are brought together by proper protein folding. Antibodies which bind to conformational epitopes will only bind to proteins folded into their proper native state (Cruse *et al.*, page 166). There are also linear epitopes, which are regions of six amino acids in the primary sequence of a protein. These are generally not found on the surface of a folded protein and are only available to antibodies upon denaturation of a protein (Cruse *et al.*, page 382). Since the instant claims involve methods of inducing an immune response specific for an organism, not antibodies specific for a particular linear protein, said antibodies must bind to a protein that is in the proper folded state and which is found on the surface of the organism, and therefore must bind to a conformational epitope. Since a conformational epitope is only found in a properly folded protein and can contain discontinuous portions of the protein, there is no way that one could determine whether a given polypeptide would bind to the antibody unless this were empirically tested. Any change (including deletions and substitutions), anywhere along the polypeptide is likely to alter the three-dimensional structure and folding of the protein, thus altering the antibody-antigen interaction. This is further supported by other authors such as McGuinness *et al.* (Mol. Microbiol., 7:505-514, 1993) and Moudallal *et al.* (EMBO Journal, 1:1005-1010, 1982), who have shown that amino acid deletions, even outside an epitope will alter protein conformation and change antibody-antigen

binding. While the proteins in the claimed composition are known, neither applicant, nor the art have shown which portions of the proteins can be altered while still maintaining the necessary epitopes to induce a bactericidal antibody response. In addition, the written description requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*.

Therefore, absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of immunoepitopes, the skilled artisan could not immediately recognize or distinguish members of the claimed genus of immunogenic compositions that elicit the induction of bactericidal antibodies directed against two or more strains of hypervirulent lineages A4, ET-5, and lineage 3 strains of serogroup B *N. meningitidis*..

Absent factual evidence, a percentage sequence similarity of less than 100 % is not deemed to reasonably support to one skilled in the art whether the biochemical activity of the claimed subject matter would be the same as that of a similar known biomolecule. It is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. Therefore, the citation of sequence similarity results in an unpredictable and therefore unreliable correspondence between the claimed biomolecule and the indicated similar biomolecule of known function and therefore lacks support regarding utility and/or enablement. Even claim 34, which recites SEQ ID NOs for each of the antigens does not meet the written description requirements because the simple presence of the antigens in the composition does not allow one to predict the immune response that will be generated.

Therefore, because the art is unpredictable, in accordance with the *Guidelines*, the description of immunoepitopes (antigenic determinants) is not deemed representative of the genus of immunogenic compositions to which the claims refer. Hence, none of the claims meet the written description requirements.

Additionally, claim 4 recites the designations "NadA" protein, "NMB1870" protein, "NMB2091" protein, "NMB1030" protein, and "NMB2132" protein. These terms constitute laboratory designations that do not convey any structural or functional limitations, and which are

not described in the specification. Therefore, the proteins to which these designations refer have not been adequately described under the requirements of 35 USC 112, first paragraph. Consequently, only a composition containing the proteins comprising the sequences of SEQ ID NO:2, 7 and 8 satisfies the written description requirements of 35 USC 112, first paragraph.

Claims 4, 6, 8, 10, 12, 14, 26, and 32-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions comprising the proteins with the sequences of NO:2, 7 and 8, does not reasonably provide enablement for the full breadth of the instant claims, for the reasons set forth in the previous office action in the rejection of claims 6, 8, 10, 12, 14, and 26.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant argues:

1. That the examiner has asserted that the broadest claim encompasses an unlimited genus of any polypeptide capable of inducing the required immune response. Applicant asserts that the broadest claim does not encompass an unlimited genus of any polypeptide, but instead encompasses a composition of (1) meningococcal polypeptides, (2) comprising at least five antigens, (3) each antigen being recited by name: NadA, NMB2091, NMB1870, NMB1030, and NMB2132, (4) the combination of five antigens being capable of inducing bactericidal antibodies against hypervirulent lineages A4, ET-5, and lineage 3 of *N. meningitidis* serogroup B. Applicant asserts that the genus is therefore not unlimited since all five antigens have been clearly described as being capable of inducing the desired immune response and preferred variants and hybrids have been referred to in the specification. Applicant also states that an exemplary composition containing all five meningococcal proteins is included in the instant disclosure. Applicant argues that the examiner's assertion is clearly not justified since it implies that the broadest claim includes not only compositions of those five meningococcal antigens and variants with all the characteristics listed above, but also includes polypeptides of other origin such as viral, human, or plant.

2. That, while the examiner has asserted that "the specification does not disclose any other compositions (or variants of the above composition) that are capable of inducing the required bactericidal antibody response," the provided working example demonstrates that combining these five proteins results in a composition with the required capabilities. Applicant argues that exemplary variants are described and references (particularly reference 16, which was incorporated by reference) evaluated these polypeptides for the ability to induce bactericidal antibodies. Applicant argues that the specification in combination with the cited references has provided sufficient guidance for one of skill in the art to generate a realistic number of compositions commensurate with the scope of the claims.

3. That applicant disagrees with the examiners assertion that the prediction of a specific immune response is unpredictable and that linear epitopes are generally not found on the surface of a protein and are only available to antibodies upon denaturation of a protein. To support their assertion, applicant states that linear epitopes are well known in native proteins and points to several examples such as the V3 epitope of HIV-1. Applicant also states that bactericidal antibodies directed to linear epitopes of serogroup B *N. meningitidis* have been reported against NMB1870 by Giuliani *et al.* and against other potentially important peptides. Applicant further argues that, while the examiner has asserted that any change, anywhere along the polypeptide is likely to alter the three-dimensional structure and folding of the protein, thus altering the antibody-antigen interaction, Giuliani *et al.* revealed with a limited amount of experimentation, the immunogenic regions of NMB1870 which allow substantial deletion of whole protein domains but still being able to induce bactericidal titers. Applicant asserts, therefore, that in view of the scientific knowledge and considering the preferred proteins disclosed in references 14-16 as indicated in the specification, there is no evidence for undue experimentation.

Applicant's arguments have been fully considered and deemed non-persuasive.

Regarding argument 1, applicant's analysis of the examiner's assertions has ignored the actual words used by the examiner. The rejection does not state that the claim is drawn to an unlimited genus of polypeptides. Instead, the rejection, discussing the breadth of the claims states that the broadest claim encompasses an unlimited genus of polypeptides *capable of inducing the required immune response*. The presence of this functional limitation was clearly recognized. In fact, the problem with the claims is that the claim has no structural limitations to

go with the functional limitation. In their description of the broadest claim, applicant has left out a very important part of the claim. For each of the five antigens, the claim states "or a variant thereof." This means that any amino acid can be altered in any way, with no limitations, while still being considered a variant of one of the five antigens listed. Therefore, so long as the polypeptide is able to induce the correct immune response, the claims do, in fact, encompass polypeptides from viruses, humans, and plants. Furthermore, as discussed above, the specification has not clearly described all five antigens as being capable of producing the required immune response. The single exemplary composition in the specification, has already been stated as being enabled. It is the unlimited other variants that one cannot simply assume will induce the correct immune response.

Regarding argument 2, it is not clear what applicant means by "a realistic number" of compositions. The fact is that the claims (at least the broadest claim) do not have *any* structural limitations and thus, the number of possible polypeptides encompassed is unlimited. Even the claims with 90 or 95% identity cover an astronomical number of possibilities. As set forth in the art and in applicant's previous arguments (in an attempt to overcome an obviousness rejection), the results of changing amino acids on the immune response generated by a polypeptide are completely unpredictable. Therefore, showing that one, or even several compositions generate the correct response does not provide any evidence that other polypeptide compositions will generate the correct immune response. As stated by the examiner, there is one composition with the required function shown in the specification. This composition is enabled. With regard to reference 16, as stated above, the reference was not properly incorporated by reference. Furthermore, the reference was not published until after the instant priority date. Enablement must be established as of the filing date. If applicant wishes to alter their priority claim to take advantage of the teachings of reference 16, they are free to do so, but until such a change is made, the teachings of reference 16 are irrelevant.

Regarding argument 3, the examiner did not simply make these assertions. The examiner's statements came directly from the art. The conformational changes that can occur from altering a peptide change are well documented (as has been shown in previously recited art). Changing amino acids even far removed from the epitope can alter the epitope. Simply citing a few, or even many linear epitopes that exist does not detract from the well known facts.

Note that the rejection (citing the art) did not say that linear epitopes are not found on the surface of a protein. Instead, it said linear epitopes are *generally* not found on the surface of a protein. If some linear epitopes are found, even these can be altered by alterations to amino acids that are far removed because if the protein folds differently, it can obscure the binding site. Furthermore, Giuliani's teachings do not support applicant's position for several reasons. First, enablement must be shown as of the filing date. As Giuliani was published several years later, the teachings therein cannot support enablement. In addition, the proteins that are combined in the instant claims are known in the art. Applicant has stressed this fact by referring multiple times to references 14-16. While reference 16 was published post-filing, the other references are prior art. Other references in the specification also teach these proteins. In fact, the examiner has previously used one of these references to reject the claims under 35 USC 103. Applicant has gone on record, using Giuliani to show that the immune response generated by combinations of these proteins is not predictable. Therefore, Giuliani does not support enablement and instead follows the rest of the art which teaches that the alteration of a given polypeptide results in an unpredictable immune response.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary.

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. Thus, Applicant assumes a certain burden in establishing

that inventions involving physiological activity are enabled. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The instant claims are drawn to compositions comprising five meningococcal antigens: an "NadA" protein, a "NMB1870" protein, a "NMB2091" protein, a "NMB1030" protein, and a "NMB2132" protein, or variants thereof, wherein the composition is able to induce a bactericidal antibody response against hypervirulent lineages A4, ET-5, and lineage 3 of *N. meningitidis* serogroup B. In addition, there are claims drawn which list the "NadA" protein as SEQ ID NO:2; the "NMB1870" protein as SEQ ID NO:3; the "NMB2091" protein as SEQ ID NO:4; the "NMB1030" protein as SEQ ID NO:5; and the "NMB2132" protein as SEQ ID NO:6.

Breadth of the claims: The broadest claim encompasses an unlimited genus of any polypeptides capable of inducing the required immune response in any animal using any means of administration or adjuvant.

Guidance of the specification/The existence of working examples: The specification discloses a working example wherein a composition comprising an NadA polypeptide with the sequence of SEQ ID NO:2, a fusion protein with the sequence of SEQ ID NO:7 (a fusion of SEQ ID NOs 6 and 5), and a fusion protein with the sequence of SEQ ID NO:8 (a fusion of SEQ ID NO:4 and 3) is capable of inducing the required immune response. However, the specification does not disclose any other compositions (or variants of the above composition) that are capable of inducing the required bactericidal antibody response.

State of the art: While the skill in the art of immunology is high, to date, prediction of a specific immune response for any given composition in any given animal is quite unpredictable. Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology. Consequently, the effects of sequence dissimilarities upon protein structure and function cannot be predicted. Bowie *et al.* (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function, carry out the instructions of the genome **and form immunoepitopes**. Bowie *et al.* further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex.

(column 1, page 1306). Bowie *et al.* further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306). Additionally, as evidenced by Greenspan *et al.* (Nature Biotechnology, 7:936-937, 1999), defining epitopes is not as easy as it seems. Greenspan *et al.* recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan *et al.*, an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows that the immunoepitopes that can elicit a particular immune response to a given pathogen can only be identified empirically. As taught in basic immunology texts, an epitope or antigenic determinant interacts with its corresponding antibody based on the three-dimensional structure of both molecules and the fit between them (Cruse *et al.*, Illustrated Dict. of Immunology, 2nd ed., CRC Press, 2003, page 46). These epitopes can be conformational (or discontinuous) epitopes which are formed from separate regions in the primary sequence that are brought together by proper protein folding. Antibodies which bind to conformational epitopes will only bind to proteins folded into their proper native state (Cruse *et al.*, page 166). There are also linear epitopes, which are regions of six amino acids in the primary sequence of a protein. These are generally not found on the surface of a folded protein and are only available to antibodies upon denaturation of a protein (Cruse *et al.*, page 382). Since the instant claims involve methods of inducing an immune response specific for an organism, not antibodies specific for a particular linear protein, said antibodies must bind to a protein that is in the proper folded state and which is found on the surface of the organism, and therefore must bind to a conformational epitope. Since a conformational epitope is only found in a properly folded protein and can contain discontinuous portions of the protein, there is no way that one could determine whether a given polypeptide would bind to the antibody unless this were empirically tested. Any change (including deletions

and substitutions), anywhere along the polypeptide is likely to alter the three-dimensional structure and folding of the protein, thus altering the antibody-antigen interaction. This is further supported by other authors such as McGuinness *et al.* (Mol. Microbiol., 7:505-514, 1993) and Moudallal *et al.* (EMBO Journal, 1:1005-1010, 1982), who have shown that amino acid deletions, even outside an epitope will alter protein conformation and change antibody-antigen binding. Applicant has asserted (backed by the 1990 Wells reference, which does not mention antigen-antibody binding) that the results of changes in the proteins of the invention are predictable. However, Blythe *et al.* (Protein Sci., 14:246-248, 2005) definitively state that one cannot reliably predict the location of epitopes. The sum of the art (both old and new) shows that with regard to generating a particular antibody response, the effects of alterations in the sequence of proteins is entirely unpredictable.

Consequently, in view of the lack of support in the art and specification, it would require undue experimentation on the part of the skilled artisan to make and use the composition as claimed; therefore, the full scope of the claims is not enabled.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian J. Gangle whose telephone number is (571)272-1181. The examiner can normally be reached on M-F 7-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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